

## ORIGINAL ARTICLE

# Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference

Andrew Kennedy<sup>1</sup>, Lourens Bester<sup>2</sup>, Riad Salem<sup>3</sup>, Ricky A. Sharma<sup>4</sup>, Rowan W. Parks<sup>5</sup> & Philippe Ruszniewski<sup>6</sup>

<sup>1</sup>Radiation Oncology Research, Sarah Cannon Research Institute, Nashville, TN, USA, <sup>2</sup>Department of Radiology, St Vincent's Public Hospital, Sydney, NSW, Australia, <sup>3</sup>Department of Radiology, Northwestern University, Chicago, IL, USA, <sup>4</sup>Oncology Department, Gray Institute, University of Oxford, Churchill Hospital, Oxford, UK, <sup>5</sup>Department of Clinical Surgery, University of Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK and <sup>6</sup>Centre for Gastroenterological and Pancreatic Disease, Beaujon Hospital, University of Paris Denis-Diderot, Paris, France

## Abstract

**Objectives:** Liver metastasis from a neuroendocrine tumour (NET) represents a significant clinical entity. A multidisciplinary group of experts was convened to develop state-of-the-art recommendations for its management.

**Methods:** Peer-reviewed published reports on intra-arterial therapies for NET hepatic metastases were reviewed and the findings presented to a jury of peers. The therapies reviewed included transarterial embolization (TAE), transarterial chemoembolization (TACE) and radioembolization (RE). Two systems were used to evaluate the level of evidence in each publication: (i) the US National Cancer Institute (NCI) system, and (ii) the GRADE system.

**Results:** Eighteen publications were reviewed. These comprised 11 reports on TAE or TACE and seven on RE. Four questions posed to the panel were answered and recommendations offered.

**Conclusions:** Studies of moderate quality support the use of TAE, TACE and RE in hepatic metastases of NETs. The quality and strength of the reports available do not allow any modality to be determined as superior in terms of imaging response, symptomatic response or impact on survival. Radioembolization may have advantages over TAE and TACE because it causes fewer side-effects and requires fewer treatments. Based on current European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines, RE can be substituted for TAE or TACE in patients with either liver-only disease or those with limited extrahepatic metastases.

Received 14 April 2014; accepted 9 July 2014

## Correspondence

Andrew S. Kennedy, Radiation Oncology Research, Sarah Cannon Research Institute, 3322 West End Avenue, Suite 800, Nashville, TN 37203, USA. Tel: + 1 615 524 4200. Fax: + 1 615 524 4700. E-mail: andrew.kennedy@sarahcannon.com

Sources of funding: NIHR Biomedical Research Centre Oxford and the Oxford Cancer Imaging Centre.

This paper is based on the NET-Liver-Metastases Consensus Conference, 12–13 December 2012, London, endorsed by the European–African Hepato-Pancreato-Biliary Association (E-AHPBA), the European Neuroendocrine Tumor Society (ENETS), the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), the European Society of Surgical Oncology (ESSO), the Great Britain and Ireland Hepato-Pancreato-Biliary Association (GBIHPBA), the International Hepato-Pancreato-Biliary Association (IHPBA) and the UK and Ireland Neuroendocrine Tumour Society (UKINETS).

## Introduction

The development of liver metastases from neuroendocrine tumours (NETs) originating in the foregut, midgut or hindgut represents a significant and frequent clinical occurrence, which negatively impacts prognosis. The management of patients with liver metastases can include surgical, medical, radiological and nuclear medicine interventions.<sup>1</sup> This broad range of possible treatments, each of which has therapeutic potential for different indications, necessitates evidence-based recommendations for the optimal management of these patients. A multidisciplinary

group of experts in the management of NET patients with liver metastases was convened in London, UK, in December 2012 to provide updated management recommendations. The International Consensus Conference on NET-Liver-Mets involved 15 individual workgroup sessions that covered a variety of topics from diagnosis to treatment. Each workgroup was comprised of recognized experts in its particular subject matter. Prior to the conference, questions were sent to the members of each workgroup to allow for deliberation and the development of statements on the workgroup topic. During the conference, a spokesperson for each workgroup presented the panel's recommendations and statements to the attendees and the conference jury. Feedback on this exchange was given to the workgroup and was considered prior to the development of the final results presented in this report. A summary of this conference has been published recently.<sup>2</sup>

For patients who are not candidates for surgery, selective hepatic transarterial embolization (TAE), transarterial chemoembolization (TACE) or radioembolization (RE) with yttrium-90 microspheres can produce objective responses, decrease tumour markers and control symptoms. However, none of these techniques has been shown to have clear superiority over the others in a randomized controlled trial (RCT). The authors of this manuscript were tasked with developing recommendations on the use of angiographic liver-directed techniques, including TAE, TACE and RE, in relation to surgery, percutaneous liver tumour ablation and systemic therapies.

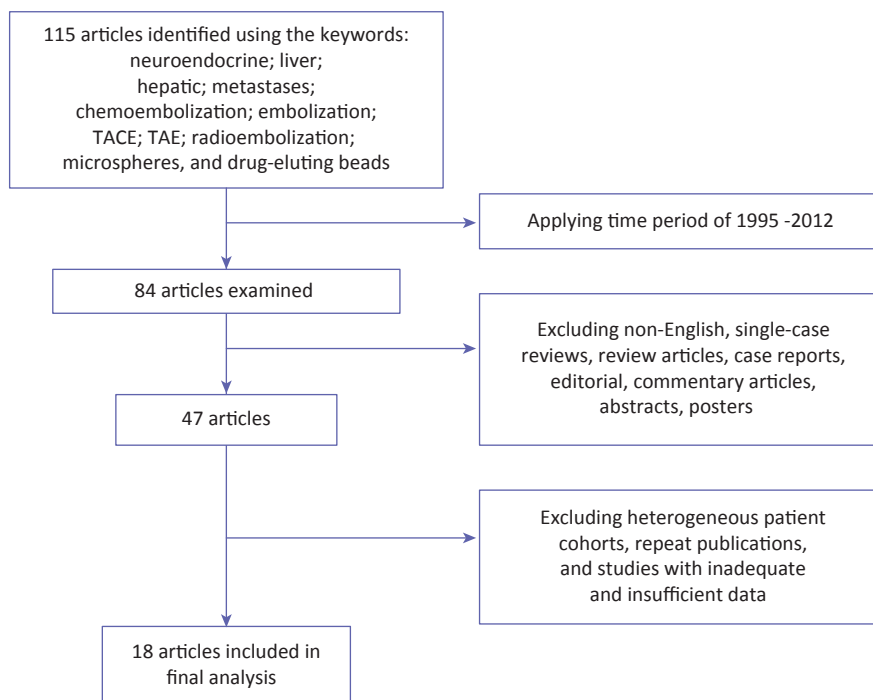
## Materials and methods

Peer-reviewed published reports on intra-arterial therapies for NET hepatic metastases were reviewed. These were presented to a multidisciplinary jury of peers for thorough discussion in order to achieve consensus recommendations. The authors were asked to consider the following questions related to percutaneous arterial liver techniques (TAE, TACE and RE) in patients with non-resectable NET liver metastases in conducting their review.

- 1 Do these techniques improve outcomes [progression-free survival (PFS), overall survival (OS) and quality of life (QoL)] in comparison with partial (R2) resection?
- 2 Which of these techniques achieves the best outcome (PFS, OS, QoL)?
- 3 Do these techniques improve outcomes in combination with systemic treatment [such as peptide receptor radiotherapy (PRRT), chemotherapy, targeted therapy, biotherapy] in comparison with percutaneous liver techniques alone?
- 4 What is the incidence of tumour dissemination during the use of TAE, TACE or RE, evident on imaging or biopsy during follow-up?

## Selection and evaluation of reports

Multiple searches of PubMed were conducted to identify published papers to December 2012 (Fig. 1). Abstracts and presentations at meetings were not included in the deliberations. The search strategy duplicated the extensive literature search



**Figure 1** Study search strategy and numbers of articles identified

**Table 1** Conversions of the National Cancer Institute (NCI) and GRADE (grading of recommendations assessment, development and evaluation) scoring systems<sup>4,5</sup> used by the present working group

NCI levels of evidence		GRADE Quality score	GRADE Strength score
<b>NCI strength of study endpoints (A–D)</b>	<b>NCI strength of study design (1–3)</b>	<b>A = highest quality study</b>	<b>1 = strong</b>
<b>A Total mortality</b> (or overall survival from a defined time)	<b>1 Randomized controlled trial</b>		
	(i) Population-based, consecutive series		
	(ii) Consecutive cases (not population-based)		
<b>B Cause-specific mortality</b> (or cause-specific mortality from a defined time)	<b>2 Non-randomized controlled trials</b>	<b>B = high quality study</b>	<b>2 = weak</b>
<b>C Carefully assessed quality of life</b>	<b>3 Case series</b>	<b>C = low quality study</b>	
	(i) Population-based, consecutive series		
	(ii) Consecutive cases, (not population-based)		
	(iii) Non-consecutive cases		
<b>D Indirect surrogates</b>		<b>D = lowest quality study</b>	
(i) Event-free survival			
(ii) Disease-free survival			
(iii) Progression-free survival			
(iv) Tumour response rate			

conducted by Yang *et al.*,<sup>3</sup> but extended the date of publication to December 2012 and accepted fewer articles for review. Two systems were used to evaluate the level of evidence and strength of endpoints of each publication: the US National Cancer Institute (NCI) medical evidence scale,<sup>4</sup> and the GRADE (grading of recommendations assessment, development and evaluation) system.<sup>5</sup>

Each of the papers selected for consideration were assigned both an NCI and a GRADE score. In addition, individual factors derived from the GRADE system were used to estimate the strength of the recommendations for each treatment modality (TAE, TACE and RE). For the purposes of report evaluation by the working group, the scoring system shown in Table 1 was used. The NCI Levels of Evidence evaluate both the strength of the study design and the strength of the study endpoints. The GRADE system considers four factors to determine the strength of a recommendation: (i) the balance between desirable and undesirable affects; (ii) the quality of the evidence; (iii) values and preferences, and, finally, (iv) costs. The quality of evidence is given a 'grade' of A, B, C or D; thus high-quality papers receive a GRADE score of A. The strength of the recommendation for or against an intervention is scored as 1 if it is strong and 2 if it is weak.

## Results

A total of 18 reports met the workgroup's stringent criteria and were reviewed by the present authors. These included 11 reports on TAE or TACE,<sup>6–16</sup> and seven on RE.<sup>17–23</sup>

Radioembolization studies are outlined in Table 2. These included four studies on the use of salvage therapy in refractory

disease and three studies conducted in mixed cohorts of patients treated with RE as either first-line treatment or in refractory disease. Four of these reports were retrospective studies. Studies on TAE and TACE are outlined in Table 3. Table 4 shows GRADE factor scoring comparisons for TAE/TACE and RE.

### Do these techniques improve outcomes (PFS, OS, QoL) in comparison with partial (R2) surgical resection?

Because data from prospective, randomized, placebo-controlled studies are lacking, the authors were unable to make a definitive statement about the superiority of percutaneous arterial liver techniques over R2 resection; neither is there sufficient evidence to indicate the use of one technique over another in terms of PFS or OS. There is some evidence to suggest that RE provides for improved QoL in comparison with TAE and TACE. The review of this literature suggests that tumour dissemination and tract seeding are not caused by the use of arterial therapies, but by direct puncture from ablation or biopsy (GRADE B1).

The consensus was to recommend that comparative studies should be conducted to adequately determine whether percutaneous arterial liver techniques offer an advantage over R2 resection (in terms of PFS, OS and QoL). These comparative effectiveness studies should include measures of costs, complications, QoL and hospital resource utilization. Other studies should compare the use of embolization techniques with that of systemic agents, and explore the utility of combinations of embolization and systemic therapy. Higher-level evidence is required before any strong recommendation on the use of embolotherapy and surgery can be made.

**Table 2** Outcomes of studies of radioembolization in patients with liver metastases from neuroendocrine tumours

Study	Patients, n	Device used	Toxicity	Radiological response (RECIST 1.0)	Survival times and rates
Rhee <i>et al.</i> <sup>22</sup>	42	Yttrium-90 (glass)	Grade III/IV (14%)	54%	Median: 22 months
		Yttrium-90 (resin)		50%	Median: 28 months
Kennedy <i>et al.</i> <sup>18</sup>	148	Yttrium-90 (resin)	33% (grade III), fatigue (6.5%)	63%	Median: 70 months
King <i>et al.</i> <sup>19</sup>	58	Yttrium-90 (resin) plus 5-FU	Radiation gastritis (2 patients), duodenal ulcer (1 patient)	39%	Median: 36 months 1-, 2- and 3-year survival: 86%, 58% and 47%, respectively
Saxena <i>et al.</i> <sup>23</sup>	48	Yttrium-90 (resin)	0.5% (grade III) 1 patient (biliary obstruction)	54%	Median: 35 months 1-, 2- and 3-year survival: 87%, 62% and 42%, respectively
Cao <i>et al.</i> <sup>17</sup>	58	Yttrium-90 (resin) plus 5-FU	Not reported	39.2%	Median: 36 months
Paprottka <i>et al.</i> <sup>21</sup>	42	Yttrium-90 (resin)	0% grade III	22.5%	Median: 95% at 16.2 months
Memon <i>et al.</i> <sup>20</sup>	40	Yttrium-90 (glass)	Fatigue (63%, all grades), nausea/vomiting (40%, all grades), grade III, IV (bilirubin, 8%; albumin, 2%; lymphocyte, 38%)	WHO: 64.0%; EASL: 71.4%	Median: 34.4 months 1-, 2- and 3-year survival: 72.5%, 62.5%, 45.0%, respectively

5-FU, 5-fluorouracil; EASL, European Association for the Study of the Liver; WHO, World Health Organization.

### Which of these techniques achieves the best outcome (PFS, OS, QoL)?

No studies directly comparing the three forms of embolotherapy were discovered, nor were any found in a search of Clinicaltrials.gov (December 2012). This is surprising because the controversy over the relative superiority of TAE and TACE is longstanding, yet no properly conducted prospective comparison study has been performed. The inherent complexities of liver embolotherapy may represent a major barrier to investigations into the outcomes of non-radioactive arterial therapies and to enquiries into the use of these therapies in comparison with RE. Therefore, no statement on which arterial therapy offers the best PFS and OS can be made. Kalinowski *et al.* completed the only QoL study in liver embolotherapy of NETs, but their study investigated only RE and included a small sample.<sup>24</sup> However, this report,<sup>24</sup> coupled with other prospective and retrospective studies,<sup>17–23</sup> suggests the acute toxicity profile of RE is lower than those of TAE or TACE.

### Do these techniques improve outcomes in combination with systemic treatment (such as PRRT, chemotherapy, targeted therapy, biotherapy) in comparison with percutaneous liver techniques alone?

No prospective or retrospective series reported the concurrent use of embolotherapy with PRRT, targeted systemic agents or biotherapy. However, two RE studies involved i.v. 5-fluorouracil (5-FU) with yttrium-90.<sup>17,19</sup> Their results suggested somewhat higher response rates and similar toxicity to that of RE alone, but both were single-arm studies with small treatment groups. No

TAE/TACE studies reported the use of systemic therapy concurrently with liver embolotherapy. There are no comparator trials of percutaneous liver tumour ablation and arterial embolotherapy in hepatic metastases from NETs and therefore no statement or recommendation can be provided.

### What is the incidence of tumour dissemination during the use of TAE, TACE or RE, evident on imaging or biopsy during follow-up?

Tumour dissemination via the direct puncture of tumour with tract seeding is not a feature of arterial therapies. There are no reports of such occurrences in the literature. The femoral artery is the only site of percutaneous entry and thus no direct contact with the tumour occurs. Conversely, locally ablative techniques and biopsies have known potential to allow tumour dissemination.

### Consensus recommendations

It is clear that higher levels of evidence are needed to refine and optimize the treatment of NET liver metastases. The panel suggests the following points should be used as a framework for future research collaborations and for the insertion of RE into an accepted treatment algorithm (Fig. 2).

- 1 Studies that compare the outcomes of the respective intra-arterial approaches should be performed. Given the disparity in post-embolization syndrome symptoms between embolotherapy and RE, these studies should include prospective QoL measures.
- 2 Studies of surgical resection in comparison with intra-arterial therapy in select patient groups should be undertaken. These

**Table 3** Outcomes of studies of transarterial embolization (TAE) and transarterial chemoembolization (TACE) in patients with liver metastases from neuroendocrine tumours (NETs)

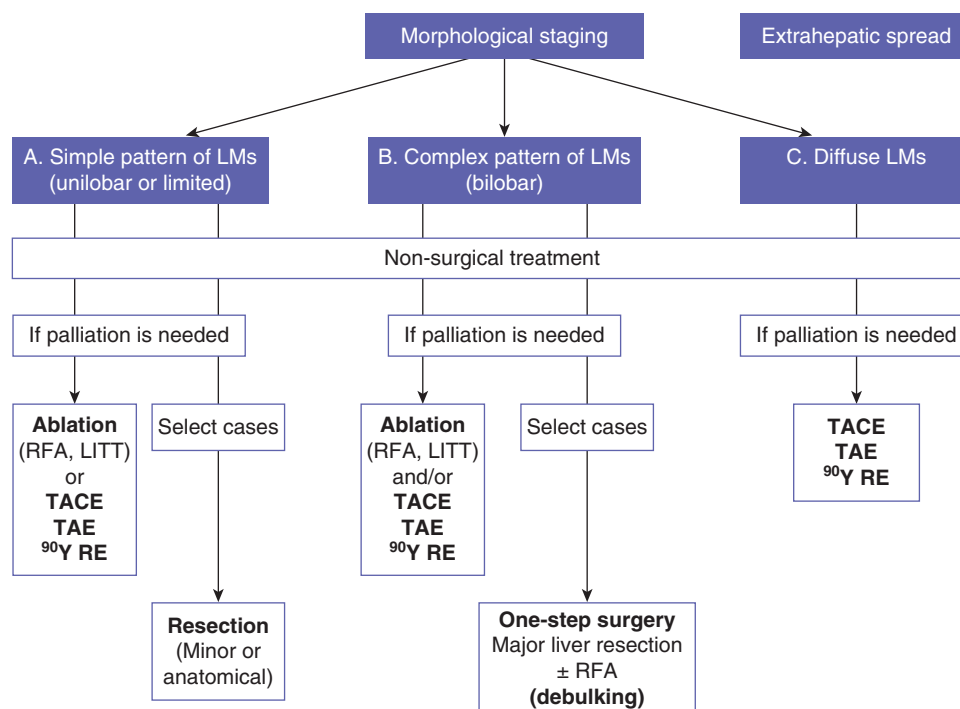
Study	Patients, <i>n</i>	Device used	Toxicity	Radiological response (RECIST 1.0)	Survival times and rates
Dong & Carr <sup>7</sup>	123	TACE	Abdominal pain (44%), diarrhoea (30%), weight loss (22%)	62%	Mean: 3.3 years 3-, 5- and 10-year survival: 59%, 36% and 20%, respectively
de Baere <i>et al.</i> <sup>6</sup>	20	TACE with doxorubicin eluting beads	Nausea (61%), fever (36%)	80%	Not reported
Vogl <i>et al.</i> <sup>16</sup>	48	TACE with mitomycin C	Nausea and vomiting (27.8%), abdominal pain (11.1%)	11.1%	Median: 38.7 months 5 years: 11.11%
		TACE with mitomycin C + gemcitabine	Nausea and vomiting (16.7%), abdominal pain (10%)	23.3%	Median: 57.1 months 5 years: 46.67%
Loewe <i>et al.</i> <sup>11</sup>	23	Bland embolization	Not reported	73%	Median: 69 months 1- and 5-year survival: 95.7% and 65.4%, respectively
Eriksson <i>et al.</i> <sup>8</sup>	41	Bland embolization	Post-embolization syndrome (all), nausea (33%), fever ( <i>n</i> = 7), median hospitalization: 12 days	50%	Median: 80 months 5 years: 60%
Pitt <i>et al.</i> <sup>13</sup>	100	Bland ( <i>n</i> = 51) versus TACE ( <i>n</i> = 49)	Bland: 7/51, (3 liver abscesses, 1 groin hematoma, 2 ileus, 1 hypotension) TACE: none	N/A	Median from diagnosis: TACE, 50.1 months; bland, 39.1 months 1-, 2- and 5-year survival: TACE, 69%, 52%, 19%, respectively; bland, 19%, 70%, 13%, respectively
Ruutinen <i>et al.</i> <sup>15</sup>	67	Bland ( <i>n</i> = 23) versus TACE ( <i>n</i> = 44)	Grade 3 or worse toxicity in 25% of TACE and 22% of bland patients TACE (≥Grade 3): pain (3); nausea (1); GET/ALP (4); AST (1), and infection (1) Bland (≥Grade 3): GET/ALP (3); AST (1), and cardiac (1)	TACE: 22% Bland: 38%	1-, 3- and 5-year survival: TACE, 86%, 67%, 50%, respectively; bland, 68%, 46%, 33%, respectively
Gupta <i>et al.</i> <sup>10</sup>	49	TACE ( <i>n</i> = 27) versus bland ( <i>n</i> = 42)	Serious adverse events in 19 patients (8.5%), hepatorenal syndrome (7), sepsis (6), transient myelosuppression (1), anasarca (1), cortical blindness (1), necrotizing cholecystitis (1), hepatic abscess (2) Overall complications: TACE, 20%; bland, 12%	TACE: 50% Bland: 25%	Median survival for carcinoid tumours: TACE, 33.8 months; bland, 33.2 months; islet tumours: TACE, 31.5 months; bland, 18.2 months
Maire <i>et al.</i> <sup>12</sup>	26	TACE ( <i>n</i> = 12) versus bland ( <i>n</i> = 14)	TACE: post-embolization syndrome (10), carcinoid crisis (2), acute liver failure (1), neutropenia (2) Bland: post-embolization syndrome (10), carcinoid crisis (0), acute liver failure (2), neutropenia (0)	TACE: 100% Bland: 92%	2-year survival: TACE, 80%; bland, 100% Median PFS: TACE, 19.2 months; bland, 23.6 months
Guiu <i>et al.</i> <sup>9</sup>	120 NET 88 HCC	DEB-TACE in HCC (with cirrhosis) and NETs (without cirrhosis)	Liver biliary injury occurred in 64/208 patients. Occurrence associated with DEB-TACE, <i>P</i> < 0.001 irrespective of tumour type	N/A	N/A
Ruzniewski <i>et al.</i> <sup>14</sup>	23	TACE	Bleeding peptic ulcer (1), oligoanuric renal failure (1), abdominal pain (50%), fever (6), nausea and vomiting (5)	PR, SD, PD, TTP 61, 22, 17, 14	8/23 died at a median of 12.5 months after final TACE

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DEB, drug-eluting beads; GGT,  $\gamma$ -glutamyl transferase; HCC, hepatocellular carcinoma; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression.

**Table 4** Summary of statements of GRADE quality and strength

Statement summary	Quality	Strength	Overall grade
1 No type of embolotherapy is most effective	Moderate	Strong	B1
2 Embolotherapy indicated for small and large tumour burdens and hormonal symptoms	Low	Weak	C2
3 Embolotherapy has the highest radiographic response rate	Low	Strong	C1
4 RE is superior to TAE/TACE in QoL and side-effects profile	Low	Weak	C2
5 By ENETS guidelines, RE is equivalent to TAE/TACE	Moderate	Strong	B1

ENETS, European Neuroendocrine Tumor Society; QoL, quality of life; RE, radioembolization; TAE, transarterial embolization; TACE, transarterial chemoembolization.



**Figure 2** Proposed treatment approach in liver-only metastases from neuroendocrine tumours. LITT, laser-induced thermotherapy; LMs, liver metastases; RE, radioembolization; RFA, radiofrequency ablation; TAE, transarterial embolization; TACE, transarterial chemoembolization;  $^{90}\text{Y}$ , yttrium-90

should investigate local control rates, but should also compare costs, complication rates, types of complication, QoL, and out-patient versus inpatient resource utilization.

- Studies investigating the outcomes of intra-arterial therapy with and without the concurrent use of systemic agents (including biologic agents) should be conducted.
- Studies of the outcomes of intra-arterial therapy in comparison with those of the use of systemic agents should be conducted in a similar fashion to that outlined in item 2.

## Discussion

Neuroendocrine tumours are uncommon but are clinically challenging tumours that occur at an annual incidence of one per

100 000 people. The current ability to produce consensus guidelines is limited by the heterogeneity of the disease itself and of the clinical studies recruiting patients with the disease. However, the development of liver metastases is the factor with the worst prognosis for patients with this disease and thus it is imperative that some statements derived from the evidence base must be attempted to guide clinicians in managing patients with liver metastases from NETs. Pavel and colleagues recently published a report on consensus guidelines for the management of liver and other distant metastases from neuroendocrine neoplasms.<sup>1</sup> The scope of the report is wide and touches on a great variety of topics, which include general management options for liver metastases. However, the current working group's charge differs in that the present authors were tasked with providing



specific and detailed opinion focused on embolotherapy of liver metastases.

Although surgical resection for metastatic NETs involving the liver is advocated by some, no prospective randomized clinical trials have compared the outcomes of this treatment modality with those in a control group or with those of other forms of therapy. In particular, there are limited data on which patients should be selected for surgery. Survival data are difficult to analyse because details on the completeness of resection, variable indications for debulking or 'palliative resection' are inadequate, and follow-up criteria are inconsistent. Complete resection (R0) rates are often low and disease-free and overall survival rates can vary widely. Despite this, 5-year survival rates of 46–86% have been reported and, in general, patients in whom hepatic resection is achievable have a better median survival and 5-year survival than those with unresectable hepatic disease.<sup>25</sup> Surgery has been postulated as the only treatment to offer potential for cure,<sup>1</sup> and favourable prognostic factors include grade 1 or 2 tumours, no evidence of non-resectable extrahepatic disease, the ability to achieve an R0 resection and the absence of carcinoid heart disease. Surgery has been shown to have a beneficial effect in alleviating symptoms related to the hypersecretion of serotonin or other mediators.<sup>26</sup>

Local ablation techniques have been used as sole treatments (performed either percutaneously or laparoscopically) or in combination with surgical resection. Histological proof of the complete destruction of tumour foci is difficult to obtain and local liver recurrence is common. Preferably, metastatic deposits should measure <5 cm in diameter, although rarely larger lesions can be targeted. Radiofrequency ablation and microwave ablation are currently the most favoured techniques and 5-year OS rates of up to 53% have been reported.<sup>2</sup> Improvements in symptom control have also been documented.<sup>27,28</sup>

Arterially directed interventional strategies provide several diverse options in the treatment of neuroendocrine liver metastases because they represent means of delivering different modalities of treatment which range from arterial embolization to cause the local ischaemia of the tumour, to the local delivery of high doses of chemotherapy to the tumour and to selective internal radiotherapy (SIRT) using yttrium-90 microspheres delivered via the arterial route. The principal clinical aims of these techniques are the reduction of hormonal symptoms in patients with functionally active tumours and the control of tumour growth and symptoms arising from tumour size.

The basis for all of the endovascular procedures discussed herein is the discovery that neuroendocrine metastases are usually highly vascular and that these metastases draw their blood supplies predominantly from the hepatic artery rather than the portal vein, whereas normal liver tissue acquires 70–80% of its blood supply from the portal vein.<sup>29</sup> An historical angle on this discovery is provided in a recent article focusing on the pathological changes resulting from SIRT.<sup>30</sup> Traditionally, transarterial therapy for liver metastases from NETs consists of TAE or TACE. In TAE, embolization is usually performed using lipiodol, gel foam parti-

cles, polyvinyl alcohol (PVA) foam or bland microspheres. If the artery supplying the tumour can be superselectively embolized, the clinical benefit to be derived by devascularizing the tumour can be achieved with a lower likelihood that a collateral blood supply will form rapidly. In clinical cases of revascularization, TAE or TACE can often be repeated.

Transarterial chemoembolization follows the same principles as TAE, but the intra-arterial administration of a chemotherapeutic agent is added at the time of embolization. This technique has the potential to result in intra-tumoral concentrations of the drug that are over 20 times greater than those afforded by the systemic administration of the same drug,<sup>31</sup> plus the potential clinical benefit of tumour ischaemia as a result of embolization. Drugs that are commonly used for this purpose include doxorubicin, melphalan and streptozocin.

Selective internal radiotherapy with yttrium-90 microspheres is a technique that has been developed to target multiple sites of disease within the liver as a form of arterially delivered brachytherapy. By contrast with surgical resection and radiofrequency ablation or other forms of local ablation, the number and sites of liver metastases do not limit its use. The technique of SIRT involves an outpatient procedure in which a transfemoral catheterization is performed and millions of radioactive microspheres (15–20 million if resin; 1–8 million if glass) are selectively released into the hepatic arterial supply under fluoroscopic guidance. This treatment preferentially delivers a high dose of radiation to the liver tumour while sparing much of the normal liver.

Bearing in mind the heterogeneity of this disease and the difficulty of defining cohorts of patients with the same pathological classification of disease, rates of symptomatic response to TAE, TACE and SIRT in the studies reviewed in the present paper would appear to be 39–95% within a time period of 1–18 months from treatment. In other words, the majority of patients do experience improvements in hormonal syndromes and the symptoms caused by the disease burden. The clinical side-effects of the procedures include fever, leukocytosis, abdominal pain and elevated liver enzyme levels. More severe complications include pleural effusion, bowel ischaemia, hepatic infarction, liver abscess and radiation-induced liver disease (SIRT only, significantly <2% of cases treated). As the occurrence of severe side-effects is uncommon, most patients who are offered intra-arterial therapies for symptom relief consent to treatment and appreciate some degree of clinical benefit.

In advocating for greater research into the use and outcomes of intra-arterial therapies for metastatic NET carcinomas, the present group emphasizes the importance of applying robust entry criteria (which should include a central histology review of all cases), of optimizing recruitment by conducting multicentre trials and ensuring adequate quality assurance of treatment across participating centres, and of considering the evolution of the standard of care during the recruitment and follow-up phases of clinical trials. For relatively rare tumours such as NETs, there may be value

in planning for combined analyses of the outcomes of several trials in order to facilitate greater statistical power. For example, FOXFIRE and SIRFLOX are both randomized multicentre trials with participating centres in Australia, New Zealand, Europe and the USA, which have evaluated the addition of yttrium-90 resin microspheres to first-line chemotherapy in patients with non-resectable liver metastases from colorectal cancer (P. Gibbs *et al.* 2014, unpublished data).<sup>32</sup> Both trials use similar chemotherapy delivery regimens with regard to the sequencing of drugs and the intra-arterial treatment intervention. Discussion between the respective development groups of the two trials led to the formulation of similar protocols and treatment paradigms in order to facilitate sufficient power for the prospective combined analysis of OS (P. Gibbs *et al.* 2014, unpublished data).<sup>32</sup>

There are ongoing controversies over the feasibility of OS studies (treatment crossover) as well as the clinical correlation between imaging responses and the manifestation of symptoms in metastases from NETs. Accordingly, the use of QoL becomes of significant interest. Although its use is still controversial, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-GINET21 tool would strengthen any study of metastases from NETs and should be considered an essential component of prospective trials. The incorporation of such a tool is relevant not only to patients with mild symptoms (flushing), but also to those afflicted by the more severe and debilitating symptoms (diarrhoea, shortness of breath).<sup>33,34</sup> These are currently being studied in prospective settings (NCT00815620, NCT00454376). Overall survival cannot be used as in other cancers because life expectancy is long and multiple treatment lines are available. Quality of life is not sensitive enough and is not affected by treatment in most RCTs. Symptomatic response, including hormone-related symptoms, is observed in 80–90% of patients, and radiological response according to RECIST (response evaluation criteria in solid tumours) in 30–50%. Although no clear correlation between these two parameters has yet been established, radiological response is almost always associated with the alleviation of symptoms.

It is fortunate that multiple treatment options for the liver-directed therapy of hepatic metastases from NETs are available. It is now the responsibility of this field to learn the optimal ways of employing local therapies to achieve the best possible QoL in patients, sustainable resource utilization, and enhanced sequencing of treatment with new systemic and biologic agents that show encouraging promise in the treatment of liver metastases from NETs.

#### Conflicts of interest

Kennedy's institution received grant funding for clinical trial from Sirtex Medical. Bester received consultancy fees from Sirtex Medical. Salem, Parks, Ruzsniowski and Sharma have no conflicts of interest.

#### References

1. Pavel M, Baudin E, Couvelard A, Krenning E, Oberg K, Steinmuller T *et al.* (2012) ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 95:157–176.
2. Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R *et al.* (2014) Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol* 15:e8–21.
3. Yang TX, Chua TC, Morris DL. (2012) Radioembolization and chemoembolization for unresectable neuroendocrine liver metastases – a systematic review. *Surg Oncol* 21:299–308.
4. National Cancer Institute. *PDQ Levels of Evidence for Adult and Pediatric Cancer Treatment Studies*. 2012. Available at <http://cancer.gov/cancertopics/pdq/levels-evidence-adult-treatment/HealthProfessional> (last accessed 1 June 2014).
5. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A *et al.* (2008) Going from evidence to recommendations. *BMJ* 336:1049–1051.
6. de Baere T, Deschamps F, Teriitheau C, Rao P, Conengraph K, Schlumberger M *et al.* (2008) Transarterial chemoembolization of liver metastases from well differentiated gastroenteropancreatic endocrine tumours with doxorubicin-eluting beads: preliminary results. *J Vasc Interv Radiol* 19:855–861.
7. Dong XD, Carr BI. (2011) Hepatic artery chemoembolization for the treatment of liver metastases from neuroendocrine tumours: a longterm follow-up in 123 patients. *Med Oncol* 28 (Suppl. 1):286–290.
8. Eriksson BK, Larsson EG, Skogseid BM, Loffberg AM, Lorelius LE, Oberg KE. (1998) Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumours. *Cancer* 83:2293–2301.
9. Guiu B, Deschamps F, Aho S, Munck F, Dromain C, Boige V *et al.* (2012) Liver/biliary injuries following chemoembolization of endocrine tumours and hepatocellular carcinoma: lipiodol vs. drug-eluting beads. *J Hepatol* 56:609–617.
10. Gupta S, Johnson MM, Murthy R, Ahrar K, Wallace MJ, Madoff DC *et al.* (2005) Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumours: variables affecting response rates and survival. *Cancer* 104:1590–1602.
11. Loewe C, Schindl M, Cejna M, Niederle B, Lammer J, Thurnher S. (2003) Permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and lipiodol: assessment of mid- and longterm results. *AJR Am J Roentgenol* 180:1379–1384.
12. Maire F, Lombard-Bohas C, O'Toole D, Vullierme MP, Rebours V, Couvelard A *et al.* (2012) Hepatic arterial embolization versus chemoembolization in the treatment of liver metastases from well-differentiated midgut endocrine tumours: a prospective randomized study. *Neuroendocrinology* 96:294–300.
13. Pitt SC, Knuth J, Kelly JM, McDermott JC, Weber SM, Chen H *et al.* (2008) Hepatic neuroendocrine metastases: chemo- or bland embolization? *J Gastrointest Surg* 12:1951–1960.
14. Ruzsniowski P, Rougier P, Roche A, Legmann P, Sibert A, Hochlaf S *et al.* (1993) Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumours. A prospective phase II study in 24 patients. *Cancer* 71:2624–2630.
15. Ruutinen AT, Soulen MC, Tuite CM, Clark TW, Mondschein JI, Stavropoulos SW *et al.* (2007) Chemoembolization and bland embolization of neuroendocrine tumour metastases to the liver. *J Vasc Interv Radiol* 18:847–855.
16. Vogl TJ, Gruber T, Naguib NN, Hammerstingl R, Nour-Eldin NE. (2009) Liver metastases of neuroendocrine tumours: treatment with hepatic



- transarterial chemotherapy using two therapeutic protocols. *AJR Am J Roentgenol* 193:941–947.
17. Cao CQ, Yan TD, Bester L, Liauw W, Morris DL. (2010) Radioembolization with yttrium microspheres for neuroendocrine tumour liver metastases. *Br J Surg* 97:537–543.
  18. Kennedy AS, Dezarn WA, McNeillie P, Coldwell D, Nutting C, Carter D *et al.* (2008) Radioembolization for unresectable neuroendocrine hepatic metastases using resin <sup>90</sup>Y-microspheres: early results in 148 patients. *Am J Clin Oncol* 31:271–279.
  19. King J, Quinn R, Glenn DM, Janssen J, Tong D, Liaw W *et al.* (2008) Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer* 113:921–929.
  20. Memon K, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Sato KT *et al.* (2012) Radioembolization for neuroendocrine liver metastases: safety, imaging, and longterm outcomes. *Int J Radiat Oncol Biol Phys* 83:887–894.
  21. Paprottka PM, Hoffmann RT, Haug A, Sommer WH, Raessler F, Trumm CG *et al.* (2012) Radioembolization of symptomatic, unresectable neuroendocrine hepatic metastases using yttrium-90 microspheres. *Cardiovasc Intervent Radiol* 35:334–342.
  22. Rhee TK, Lewandowski RJ, Liu DM, Mulcahy MF, Takahashi G, Hansen PD *et al.* (2008) <sup>90</sup>Y Radioembolization for metastatic neuroendocrine liver tumours: preliminary results from a multi-institutional experience. *Ann Surg* 247:1029–1035.
  23. Saxena A, Chua TC, Bester L, Kokandi A, Morris DL. (2010) Factors predicting response and survival after yttrium-90 radioembolization of unresectable neuroendocrine tumour liver metastases: a critical appraisal of 48 cases. *Ann Surg* 251:910–916.
  24. Kalinowski M, Dressler M, Konig A, El-Sheik M, Rinke A, Hoffken H *et al.* (2009) Selective internal radiotherapy with yttrium-90 microspheres for hepatic metastatic neuroendocrine tumours: a prospective single centre study. *Digestion* 79:137–142.
  25. Frilling A, Li J, Malamutmann E, Schmid KW, Bockisch A, Broelsch CE. (2009) Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. *Br J Surg* 96:175–184.
  26. Sarmiento JM, Que FG. (2003) Hepatic surgery for metastases from neuroendocrine tumours. *Surg Oncol Clin N Am* 12:231–242.
  27. Berber E, Flesher N, Siperstein AE. (2002) Laparoscopic radiofrequency ablation of neuroendocrine liver metastases. *World J Surg* 26:985–990.
  28. Eriksson J, Stalberg P, Nilsson A, Krause J, Lundberg C, Skogseid B *et al.* (2008) Surgery and radiofrequency ablation for treatment of liver metastases from midgut and foregut carcinoids and endocrine pancreatic tumours. *World J Surg* 32:930–938.
  29. Vogl TJ, Naguib NN, Zangos S, Eichler K, Hedayati A, Nour-Eldin NE. (2009) Liver metastases of neuroendocrine carcinomas: interventional treatment via transarterial embolization, chemoembolization and thermal ablation. *Eur J Radiol* 72:517–528.
  30. Wang LM, Jani AR, Hill EJ, Sharma RA. (2013) Anatomical basis and histopathological changes resulting from selective internal radiotherapy for liver metastases. *J Clin Pathol* 66:205–211.
  31. Roche A, Girish BV, de Baere T, Baudin E, Boige V, Elias D *et al.* (2003) Trans-catheter arterial chemoembolization as first-line treatment for hepatic metastases from endocrine tumours. *Eur Radiol* 13:136–140.
  32. Dutton S, Kenealy N, Love S, Wasan H, Sharma R, Group FP *et al.* (2014) Study protocol: FOXFIRE: an open-label, randomized, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional selective internal radiation therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer. *BMC Cancer* 14:497.
  33. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. (2011) Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumours treated with [<sup>177</sup>Lu-DOTA<sup>0</sup>,Tyr<sup>3</sup>]octreotate. *J Nucl Med* 52:1361–1368.
  34. Yadegarfar G, Friend L, Jones L, Plum LM, Ardill J, Taal B *et al.* (2013) Validation of the EORTC QLQ-GINET21 questionnaire for assessing quality of life of patients with gastrointestinal neuroendocrine tumours. *Br J Cancer* 108:301–310.